08/418,870

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/418,870	04/07/95	VAN NEST	G 0085 006

EXAMINER: AUER, H
ART UNIT: 1813 | PAPER NUMBER: 35

18N1/0214

BARBARA G MCCLUNG
CHIRON CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT R440
P O BOX 8097
EMERYVILLE CA 94662-8097

DATE MAILED: 02/14/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 04/07/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-9, 29 and 36 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-9, 29 and 36 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1. Claims 1-9, 29 and 36 are pending in the instant application, claims 10-28 and 30-35 having been cancelled in earlier amendments, and claim 36 having been added in the amendment filed Dec. 22, 1994, paper 28.

2. Applicants are requested to amend the specification updating the current status of parent applications.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as not describing the invention, nor the manner of making it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains to make and use the same.

The specification recites on p. 17, l. 17-19, "An adjuvant composition of the invention *consists essentially of* a metabolizable oil in water and an emulsifying agent...." (emphasis added). This statement indicates that the essential properties of the composition are conferred by the metabolizable oil in water and the emulsifying agent. Yet on p. 17, l. 23-30 is found, "However, increased immunostimulating activity can be provided by including any of the known immunostimulating agents in the composition. These...can either be separate from the emulsifying agent and the oil or...can be one and the same molecule. And on p. 18, l. 19-20 is found "The preferred immune-response-stimulating muramyl peptides...", and further on p. 23, l. 19-28 is presented "a number of preferred amphipathic immunostimulating peptides". Furthermore, virtually every working example in the specification includes MTP-PE, an example of an amphipathic immunostimulating peptide which is a muramyl peptide, *in addition to nonionic detergent emulsifying agents*. The presence of these muramyl peptides or their derivatives is in contradiction to the use of the term "consisting essentially of" an oil and an emulsifying agent, for the muramyl peptides critically alter the essential aspects of the adjuvant properties of the composition.

In conclusion, the specification does not enable an adjuvant composition comprising a metabolizable oil and an emulsifying agent fulfilling the limitations of the claim in the absence of MTP-PE.

4. Claims 1-9, 29 and 36 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification, as set out in Item 3.

5. The specification is objected to under 35 U.S.C. § 112, first paragraph, as not describing the invention, nor the manner of making it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains to make and use the same.

Several working examples are presented in the specification. Because of the very broad animal-to-animal variability, and the small sample sizes used, it is difficult to determine whether the invention is successful in eliciting antibody responses when immunizations are conducted with antigens suspended in a claimed adjuvant, raising a question of predictability of the outcome of making and/or using the invention. These observations are slightly mitigated by the results given in the Declaration under 37 CFR 1.132 filed Dec. 22, 1994, although, in this case, only the average results, rather than those for individual animals, have been presented. The unpredictability of the invention as exemplified in the specification indicates that a worker skilled in the art would need to engage in undue experimentation to make and use the claimed invention with predictable results.

6. Claims 1-9, 29 and 36 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification as presented in Item 5.

7. Claims 1-9, 29 and 36 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to adjuvant composition incorporating MTP-PE. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Independent claim 1 recites an adjuvant composition *comprising* a metabolizable oil and an emulsifying agent. This is not supported by the use of the term "consisting essentially above" in the specification, because virtually every working example includes in addition MTP-PE, a

substance which changes the essential emulsion-forming and adjuvant properties of the composition.

8. Claims 1-9, 29 and 36 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
In claim 1, the phrase "does not require muramyl peptides" is vague and indefinite. The phrase suggests that muramyl peptides either may optionally be included, or omitted, all with equal effect on the operation of the invention. The claim must particularly point out and distinctly claim the invention. In conformity with the election of Group I of the restriction requirement presented in Paper 4, claim 1 should *specifically recite omitting muramyl peptides* as an element, or else the phrase "does not require muramyl peptides" should be deleted. Applicants should note that the Examiner is not inviting claim language that would result in including muramyl peptides, for that would contravene Applicants' election of Group I of the restriction requirement presented in Paper 4.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 5, 6, and 9 are rejected under 35 U.S.C. § 102(b) as being anticipated by Mizushima et al., U. S. Patent No. 4,613,505 (Mizushima et al.). Mizushima et al. presents pharmaceutical formulations containing vegetable oils and phospholipids including phosphatidylcholine and phospatidylethanolamine as emulsifiers. The emulsion is prepared using a Manton-Gaulin press and produces oil droplets less than 1.0 μm in diameter (col. 3, l. 26-30, 43, and 57-60; col. 4, l. 58-64). A composition including 15% oil in water, with a phospholipid content of 1.8%, is described (col. 6, l. 62-col. 7, l. 11).

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

12. Claims 1-9 and 29 are rejected under 35 U.S.C. § 103 as being unpatentable over Hoskinson et al., U. S. Patent No. 5,109,026 (Hoskinson et al.) in view of Mizushima et al. Hoskinson et al. discloses an immunoadjuvant composition based on oils, including squalene, and Arlacel products including Arlacel A or Arlacel 80, or Tween 80, as emulsifiers. The range of volume ratios of oil to water range from 20:80 to 80:20, spanning o/w as well as w/o emulsions. (Col. 3, l. 23-44, and col. 6, l. 13-28). The resulting compositions are used to vaccinate sheep, which develop antibodies to antigen as a result. Hoskinson et al. lacks a vegetable oil as a possible oil component, and does not specify an oil droplet size in the resulting emulsion.

As noted above, Mizushima et al. reports a submicron-sized o/w emulsion based on vegetable oil and phospholipids, which is intended for intravenous injection of active agents, resulting in strong pharmacological activity and a long-lasting pharmacological effect in small doses (col. 2, l. 44-56).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare o/w emulsions based on oils such as squalene or other terpenoids or animal oils, and on nonionic detergents such as Arlacel, as taught by Hoskinson et al., or to employ vegetable oils as disclosed by Mizushima et al., and to emulsify them to submicron droplet size using a device such as a Manton-Gaulin press, because Mizushima et al. teaches that such preparations have beneficial pharmacological effects when injected into a host animal, with a reasonable expectation of success, without undue experimentation, and without requiring the teachings of Applicants.

13. Claim 36 is rejected under 35 U.S.C. § 103 as being unpatentable over Hoskinson et al. and Mizushima et al., as applied to claims 1-9 and 26 above, and further in view of Glass et al., U. S. Patent No. 3,919,411 (Glass et al.).

Glass et al. discloses an adjuvant preparation containing a combination of nonionic detergents, polyoxyethylene sorbitan monooleate and sorbitan monolaurate, in an o/w emulsion based on cottonseed oil. Glass et al. states that art workers will appreciate that routine testing may be required in order to optimize a given emulsion system for a particular usage (col. 6, l. 9-12), and furnish a large number of exemplary binary combinations of detergents as emulsifiers (col. 12, Example IV, col. 14, Example VI).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare o/w emulsions based on animal or vegetable oils, and on nonioinc detergents, as taught by Hoskinson et al. and by Mizushima et al. above, to emulsify them to submicron droplet size using a device such as a Manton-Gaulin press, and further to combine the nonionic detergents polyoxyethylene sorbitan monooleate and sorbitan monolaurate, as disclosed in numerous particular examples by Glass et al., with a reasonable expectation of success, without undue experimentation, and without requiring the teachings of Applicants.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group Art Unit 1813 Fax number is (703) 305-7939 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Henry E. Auer, Ph. D., whose telephone number is (703) 308-4240. The examiner can normally be reached Monday-Friday from 8:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christine Nucker, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

HEA
Henry E. Auer, Ph. D.
February 9, 1996

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800